REMARKS

A. Regarding the Amendments

In accordance with the present invention, there are provided methods for treating mitochondrial disorders comprising administering to a subject in need thereof an effective amount of a pyrimidine-based nucleoside. Invention methods are particularly effective in treating conditions in which there is a decrease in pyrimidine biosynthesis. Accordingly, invention methods are useful for treating a variety of pathological conditions caused by defects in mitochondrial function that include, but are not limited to, primary disorders of oxidative phosphorylation, such as, mitochondrial encephalomyopathy with lactic academia and stroke-like episodes (MELAS), and the like.

By the present communication, claims 1, 6, 7, 20, 21, 25, 28, 29, 38, 43-46, 54-57, and 62 have been amended and claim 66 has been added. It is noted that claims 28-65 were added by the Request For Interference Under 37 C.F.R § 1.604 filed on June 27, 2002. These claims were added to define Applicant's invention with greater particularity and not in response to any properly cited reference. Claims 1, 6, 7, 20, 21, 25, 28, 29, 38, 43-46, 54-57, and 62 have been amended as set forth in the attached "Version With Markings To Show Changes Made" (Exhibit A). Also included is a listing of the claims upon entry of the present response (Exhibit B). As amended, the claims are supported by the specification and the original claims and add no new matter. In addition, please cancel claims 47-53, 58-61, and 63-65 without prejudice. Upon entry of the amendments, claims 1-46, 54-57, 62, and 66 will be pending.

B. Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-25 and 27 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim subject matter which Applicant regards as the invention, is respectfully traversed. With specific reference to claim 4, Applicant respectfully disagrees with the Examiner's assertion that there is allegedly insufficient antecedent basis in claims 1 and 2 for the phrase "carbonyl derivative of an amino acid". It is respectfully submitted that the Examiner has taken the subject phrase out of context in efforts to

demonstrate alleged insufficient antecedent basis. Indeed, it is clear that this phrase, as it appears within the context of claim 4, further defines the "alkyl carbonyl" which is explicitly set forth in claim 1 (upon which claim 4 depends).

Similarly, with specific reference to claim 5, Applicant respectfully disagrees with the Examiner's assertion that there is allegedly insufficient antecedent basis in claim 1 for the phrase "carbonyl derivative of a dicarboxylic acid". It is respectfully submitted that the Examiner has taken the subject phrase out of context in efforts to demonstrate alleged insufficient antecedent basis. Indeed, this phrase, as it appears within the context of claim 5, further defines the "alkyl carbonyl" which is explicitly set forth in claim 1 (upon which claim 5 depends). Thus, antecedent basis clearly exists for the phrases "carbonyl derivative of an amino acid" and carbonyl derivative of a dicarboxylic acid", as these phrases appear in claims 4 and 5, respectively.

With specific reference to claims 1 and 25, it is respectfully submitted that these claims are clear and unambiguous as written. Nevertheless, the amendments to these claims presented herein more particularly define the substitution scheme with respect to the alkyl, alkenyl, and alkynyl moieties recited in claims 1 and 25, thereby removing any alleged ambiguity with respect to these claims.

For all of the above reasons, it is respectfully submitted that claims 1-25 and 27 are clear and unambiguous. Accordingly, reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. 112, second paragraph, are respectfully requested.

The rejection of claims 4 and 5 under 35 U.S.C. 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, is respectfully traversed. Applicant respectfully disagrees with the Examiner's assertion that Applicant has allegedly failed to define the phrases "carbonyl derivative of an amino acid" and "carbonyl derivative of a dicarboxylic acid" (as these phrases appear in claims 4 and 5, respectively). Contrary to the Examiner's assertion, the specification explicitly sets forth definitions for each of these phrases (see specification, page 5, line 20 to page 6, line 5). In

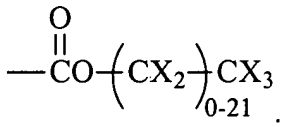
addition to these definitions, exemplary compounds are provided (see specification, page 6, lines 1-9) to assist in providing a clear and concise definition of the subject phrases. Based on this disclosure, those skilled in the art can readily determine compounds which fall within or without the scope of claims 4 and 5. Thus, the Examiner's assertion that the metes and bounds of these claims cannot be precisely determined is respectfully submitted to be in error. Accordingly, reconsideration and withdrawal of the rejection of claims 4 and 5 under 35 U.S.C. 112, second paragraph are respectfully requested.

C. Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 4 and 5 under 35 U.S.C. 112, first paragraph, as containing subject matter which is allegedly not described in such full, clear, concise, and exact terms as to enable any person skilled in the art to make and or use the invention, is respectfully traversed. Applicant respectfully disagrees with the Examiner's assertions that "numerous compounds that lack enablement and an adequate teaching as to how to prepare them" are allegedly encompassed in claims 4 and 5, and that "undue experimentation" is allegedly required to embrace the scope of the claims. Contrary to the Examiner's assertion, the specification explicitly sets forth definitions for both a "carbonyl derivative of an amino acid" and "carbonyl derivative of a dicarboxylic acid" (see specification, page 5, line 20 to page 6, line 5). In addition to these definitions, exemplary compounds are provided (see specification, page 6, lines 1-9) to assist in providing a clear and concise definition of the subject phrases. Those skilled in the art recognize that these carbonyl derivatives can be readily prepared using straightforward reaction chemistry found in any organic chemistry textbook. Since the aforementioned carbonyl derivatives of amino acids and carboxylic acids are well-recognized by those skilled in the art, undue experimentation is clearly not required to practice the invention as defined by claims 4 and 5. Thus, it is respectfully submitted that the rejection of claims 4 and 5 under 35 U.S.C. 112, first paragraph, is not properly applied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The rejection of claims 1, 3-25, and 27 under 35 U.S.C. 112, first paragraph, as being based on a disclosure which is allegedly not enabling, is respectfully traversed. Specifically, the

Examiner asserts that the groups "X_2" and "X_3" within the definition of R_2 in Formula (I) are not defined, thereby resulting in claims which are allegedly not enabled. It is respectfully submitted that the Examiner has misinterpreted the substructure containing the substituent "X" in claims 1 and 25 (this substructure is reproduced below):



In this substructure, those skilled in the art recognize that CX_2 and CX_3 refer to a methylene unit and a methyl unit, respectively. With specific reference to the methylene unit, the subscript "2" refers to the two "X" substituents attached to the methylene carbon atom. Similarly, with specific reference to the methyl unit, the subscript "3" refers to the three "X" substituents attached to the methyl carbon atom. Indeed, there are no distinct moieties "X_2" or "X_3" contemplated by claims 1 and 25. Instead, there is only one variable, namely, "X", contemplated by the substructure in claims 1 and 25. Thus, since there are no groups labeled "X_2" or "X_3" contemplated by the substructure in claims 1, it is respectfully submitted that this rejection is moot. Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3-25 and 27 under 35 U.S.C. 112, first paragraph, are respectfully requested.

D. Rejection Under 35 U.S.C. § 102

The rejection of claims 1, 7, 25, and 27 under 35 U.S.C. 102(b) as allegedly being anticipated by Isono, et. al., (Japanese Patent No. 53056690), and the rejection of claims 1-7 and 25-27 under 35 U.S.C. 102(e) as allegedly being anticipated by von Borstel, et. al. (U.S. Patent No. 6,258,795), are respectfully traversed. Applicant's invention, as defined, for example, by claim 1, distinguishes over each of the cited references by requiring a method for the treatment of a mitochondrial disorder comprising administering to a subject having or at risk of having such disorder an effective amount of a well-defined pyrimidine-based nucleoside. Neither of the cited references describe such a method.

Applicant respectfully disagrees with the Examiner's characterization of Isono and von Borstel as allegedly teaching methods for treating mitochondrial disorders. Contrary to the Examiner's assertion, those skilled in the art would readily acknowledge that, as of the filing dates of each of these references, the conditions set forth in either of the references (see, for example, von Borstel col. 10, lines 44-55) were not understood to be associated with mitochondrial defects. Indeed, both of the cited references are silent with respect to methods for treating mitochondrial disorders. Accordingly, it is only with the benefit of improper hindsight analysis that Isono and von Borstel can be characterized as allegedly teaching methods for treating mitochondrial disorders.

Mitochondrial disorders, as defined by the present specification, refer to disorders of mitochondrial metabolism that arise from a genetic defect in nuclear or mitochondrial DNA. These disorders may be inherited (i.e., primary disorders) or acquired as somatic mutations (i.e., secondary disorders), and may be caused by physiologic effects of drugs, viruses, certain othe rinfections, or environmental toxins on mitochondrial function. Clearly, the present invention provides a fundamental understanding of the connection between mitochondrial disorders and the manifestation of disease states caused thereby. For example, only the present invention recognizes that genetic defects in mitochondrial or nuclear DNA, or physiologic inhibition of mitochondrial function, are the root causes of the pathological conditions set forth in the specification (see specification, page 7, lines 1-29). In addition, only the present invention recognizes that, as a result of these genetic and physiologic defects, subjects afflicted with the pathological conditions set forth in the specification exhibit an inability to produce sufficient pyrimidines since *de novo* synthesis of pyrimidines is coupled to and requires normal mitochondrial electron transport function. Finally, only the present invention recognizes that the conditions set forth in the specification can be effectively treated by administration of pyrimidine-based nucleosides. All of this insight into mitochondrial disorders was unavailable to those skilled in the art as of the filing dates of Isono and von Borstel. Thus, it is respectfully submitted that neither of these references anticipate the present invention, and that the rejections under 35 U.S.C.§102 are not properly applied. Accordingly, reconsideration and withdrawal of

the rejection of claims 1, 7, 25, and 27 under 35 U.S.C.§102(b) and the rejection of claims 1-7 and 25-27 under 35 U.S.C.§102(e) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge additional claim fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: July 15, 2002

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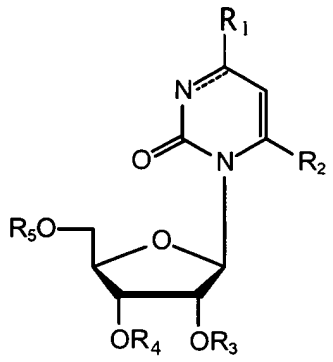
Exhibit A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for the treatment of a mitochondrial disorder comprising administering to a subject having or at risk of having such disorder an effective amount of a compound of Formula I:

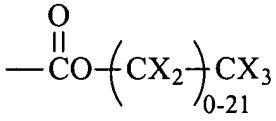


(I)

wherein:

R_1 is O, OH or NH_2,

R_2 is H, CO_2H, or



wherein:

each X is independently H or optionally substituted C_1-C_{22} alkyl, optionally substituted C_1-C_{22} alkenyl or optionally substituted C_1-C_{22} alkynyl, with substituents selected from the group consisting of H, **[C_{1-3}]** C_1-C_3 alkyl, OH, NH_2, and halogen, **[or wherein X is H,]**

R_3, R_4, and R_5 are**[,]** each independently**[,]** optionally substituted C_1-C_{22} alkyl carbonyl, with substituents selected from the group consisting of **[C_{1-3}]** C_1-C_3 alkyl, OH, NH_2, and halogen, **[and]** or H, wherein at least one of R_3, R_4, and R_5 is not H,

thereby treating the disorder.

6. (Amended) A method according to claim 1, wherein the mitochondrial disorder is a primary disorder comprising at least one **[comprises a]** mutation in mitochondrial or nuclear DNA.

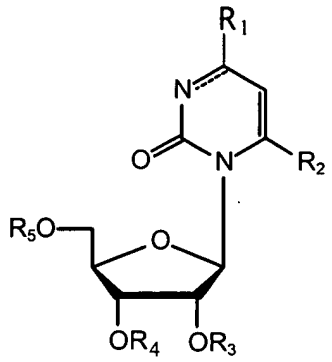
7. (Twice Amended) A method according to claim 1 or claim 2, wherein the mitochondrial disorder is selected from the group consisting of Huntington's disease, Amyotrophic lateral sclerosis, MELAS (Mitochondrial encephalomyopathy with lactic acidemia and stroke-like episodes), MERRF (Myoclonus, epilepsy, and myopathy with ragged red fibers), NARP/MILS (Neurogenic muscular weakness, ataxia, retinitis pigmentosa/Maternally inherited Leigh syndrome), LHON (Lebers hereditary optic neuropathy) "Mitochondrial blindness", KSS (Kearns-Sayre Syndrome), PMPS (Pearson Marrow-Pancreas Syndrome), CPEO (Chronic progressive external opthalmoplegia), Leigh syndrome, Alpers syndrome, Multiple mtDNA deletion syndrome, MtDNA depletion syndrome, Complex I deficiency, Complex II (SDH) deficiency, Complex III deficiency, Cytochrome c oxidase (COX, Complex IV) deficiency, Complex V deficiency, Adenine Nucleotide Translocator (ANT) deficiency, Pyruvate dehydrogenase (PDH) deficiency, pyruvate carboxylase deficiency, Ethylmalonic aciduria with

lactic acidemia, 3-Methyl glutaconic aciduria with lactic acidemia, Refractory epilepsy with declines during infection, Asperger syndrome with declines during infection, Autism with declines during infection, Attention deficit hyperactivity disorder (ADHD), Cerebral palsy with declines during infection, Dyslexia with declines during infection, **[maternally inherited thrombocytopenia and leukemia syndrome,]** MNGIE (Mitochondrial myopathy, peripheral and autonomic neuropathy, gastrointestinal dysfunction, and epilepsy), MARIAHS syndrome (Mitochondrial ataxia, recurrent infections, aphasia, hypouricemia/hypomyelination, seizures, and dicarboxylic aciduria), ND6 dystonia, Cyclic vomiting syndrome with declines during infection, 3-Hydroxy isobutryic aciduria with lactic acidemia, Diabetes mellitus with lactic acidemia, Familial Bilateral Striatal Necrosis (FBSN), Aminoglycoside-associated deafness, Dilated or hypertrophic cardiomyopathy, **[Splenic Lymphoma,]** Wolfram syndrome, Multiple mitochondrial DNA deletion syndromes, and Renal Tubular Acidosis/Diabetes/Ataxi**[s]**a syndrome.

20. (Amended) A method according to claim 19, wherein the co-factor is one or both of Coenzyme Q10 or calcium pyruvate.

21. (Amended) A method according to claim 19, wherein the vitamin is selected from the group consisting of thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate, cyanocobalamine (B12), biotin, α-lipoic acid and pantothenic acid.

25. (Amended) A method for reducing or eliminating one or more symptoms associated with a mitochondrial disorder comprising administering to a subject in need thereof an effective amount of a compound of Formula I:

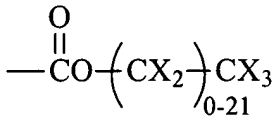


(I)

wherein:

R_1 is O, OH or NH_2,

R_2 is H, CO_2H, or



wherein:

each X is independently H or optionally substituted C_1-C_{22} alkyl, optionally substituted C_1-C_{22} alkenyl or optionally substituted C_1-C_{22} alkynyl, with substituents selected from the group consisting of H, **[C_{1-3}]** C_1-C_3 alkyl, OH, NH_2, and halogen, **[or wherein X is H,]**

R_3, R_4, and R_5 are**[,]** each independently**[,]** optionally substituted C_1-C_{22} alkyl carbonyl, with substituents selected from the group consisting of **[C_{1-3}]** C_1-C_3 alkyl, OH, NH_2, and halogen, **[and]** or H, wherein at least one of R_3, R_4, and R_5 is not H,

thereby treating the disorder.

28. (Amended) A method according to claim 1 or 2, wherein the mitochondrial disorder is selected from the group consisting of MELAS (mitochondrial encephalomyopathy with lactic acidemia and stroke-like episodes), MERRF (myoclonus, epilepsy, and myopathy with ragged red fibers), NARP/MILS (neurogenic muscular weakness, ataxia, retinitis pigmentosa/maternally inherited Leigh syndrome), LHON (Lebers hereditary optic neuropathy, "mitochondrial blindness"), KSS (Kearns-Sayre Syndrome), PMPS (Pearson Marrow-Pancreas Syndrome), CPEO (chronic progressive external opthalmoplegia), Leigh syndrome, Alpers syndrome, multiple mtDNA deletion syndromes, mtDNA depletion syndromes, complex I deficiency, ND6 dystonia, complex II (SDH) deficiency, complex III deficiency, cytochrome C oxidase (COX, complex IV) deficiency, complex V deficiency, adenine nucleotide translocator (ANT) deficiency, pyruvate carboxylase dediciency, and pyruvate dehydrogenase (PDH) deficiency.

29. (Amended) A method for treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction in a mammal comprising administering to said mammal in need of such treatment or prevention an effective amount of a pyrimidine **[nucleotide]** nucleoside.

38. (Amended) A method as in claim 37 wherein said congenital mitochondrial disease is selected from the group consisting of MELAS, LHON, MERRF, MNGIE, NARP, PEO, Leigh's Disease, Alpers syndrome, mitochondrial cytopathy, mitochondrial myopathy, mitochondrial encephalomyopathies, and **[Keams-Sayres]** Kearns-Sayre Syndrome.

43. (Amended) A method as in claim 29 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is selected from the group consisting of renal tubular acidosis, dilating or hypertrophic cardiomyopathy, steatohepatitis, hepatic failure, and lactic acidemia.

44. (Amended) A method for treating developmental delay in cognitive, motor, language, executive function, or social skills in a mammal comprising administration of an effective amount of a pyrimidine **[nucleotide]** nucleoside.

45. (Amended) A method as in claim 44 wherein said developmental delay is a subset of Attention Deficit/Hyperactivity Disorder.

46. (Amended) A method as in claim 44 wherein said developmental delay is a subset of autism associated with mitochondrial dysfunction.

54. (Amended) A method as in claim **[47]** 29 wherein said pyrimidine **[nucleotide precursor]** nucleoside is selected from the group consisting of uridine, cytidine, an acyl derivative of uridine, an acyl derivative of cytidine, orotic acid, an alcohol ester of orotic acid, or a pharmaceutically acceptable salt thereof.

55. (Amended) A method as in claim 54 wherein said pyrimidine **[nucleotide precursor]** nucleoside is administered orally.

56. (Amended) A method as in claim **[47]** 29 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is a congenital mitochondrial disease.

57. (Amended) A method as in claim 56 wherein said congenital mitochondrial disease is selected from the group consisting of MELAS, LHON, MERRF, NARP, PEO, Leigh's Disease, Alpers syndrome, and Kearns-Sayres Syndrome.

62. (Amended) A method as in claim 47 wherein said pathophysiological consequence of mitochondrial respiratory chain dysfunction is selected from the group consisting of renal tubular acidosis, dilating or hypertrophic cardiomyopathy, steatohepatitis, hepatic failure, and lactic acidemia.